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REMARKS

Claims 1-55 and 59 are pending in the subject application. Claims 56-58 have been withdrawn without prejudice because they are drawn to a non-elected invention. Claims 1, 12, 14, 18, 22, 28, 31, 33, 34, 47, 48, and 59 have been amended for clarification and for correcting typographical errors. Support for the amendments to the claims is found throughout the specification as filed and no new matter is presented by the amendments. Claim 54 has been canceled without prejudice.

Favorable reconsideration in light of the amendments and remarks, which follows is respectfully requested.

Applicants respond to the prior Office Action as follows.

1. Objections to the Specification

The Examiner objected to the Abstract for not completely describing the disclosed subject matter. As suggested by the Examiner, the full name of the enzymes has been included for completeness. The Examiner also objected to two typographical errors on page 45 of the specification. As suggested, they have also been corrected.

The Examiner asserts that the description of the elongation/cyclization method found in the specification on page 45 and depicted in Figure 3c, is confusing. The Examiner asserts that in the “excised” version, no PCP domain is present so it is unclear how dimerization is occurring.

Figure 3c is clear to one of ordinary skill in the art based on the specification as a whole.

One reading the description of Figure 3c in context would understand the role of the PCP domain, especially when read in light of Figure 3b, which immediately precedes it.

The Examiner asserts that the description of methods using thioester substrates wherein one or more of the amide linkages between residues has been placed with ester linkages on page 46 of the specification implies that data was collected, but that none is actually mentioned.

Applicants believe that the specification as filed provides ample indication that the compounds 22, 23, 25, and 27 were cyclized by excised tyrocidine synthetase TE domain to provide a macrocycle product. However, in the interest of advancing prosecution, the language “data not show” has been incorporated into the specification as suggested by the Examiner.

Accordingly, applicants request the Examiner to withdraw the objections to the specification.

2. Claim Objections

The Examiner objected to claim 18 for having two sentences. As suggested by the Examiner, the informality has been corrected.

Claim 48 is objected to for containing a typographical error in claim dependence. Claim 48 has been corrected as suggest by the Examiner to depend from claim 47.

Claim 54 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants have canceled claim 54 without prejudice.

Accordingly, the objections to claims 18 and 48 should be withdrawn and the claims allowed.

3. 35 U.S.C. §112, 2nd Paragraph Rejections

Claims 1-55 and 59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse these rejections.

Claim 1 has been rejected for containing the abbreviation "TE" without definition upon its first appearance. As suggested by the Examiner suggests, the claim has been corrected to recite "thioesterase (TE) domain protein" for clarity.

Claims 4 and 37 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "weakly-nucleophilic" is unclear. The term "weakly-nucleophilic is a well known term in the art and is not unclear to one of ordinary skill in the art. For example, many issued U.S. Patents, including, US Pat Nos. 6,590,117; 6,326,494; and 6,312,818 all use the term "weakly-nucleophilic" in their claims without defining the term in their specifications. Thus, this evidence suggests that the term "weakly nucleophilic" is clear to one of skill in the art.

Claims 6-8 and 39-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the phrases "about 5" and "about 7" in reference to the pH are unclear as to their scope.

The Examiner states that the ordinarily skilled artisan cannot ascertain the scope of the claims from any variability in the examples. The metes and bounds are not clear in the claims,

and the specification does not aid in the interpretation of the term "about". As the Federal Circuit has held, the term "about" is not a precise term and is "dependent on the facts of the case, the nature of the invention, and the knowledge imparted by the totality of the earlier disclosure to those skilled in the art." See *Eiselstein v Frank*, 52 F. 3d 1035, 1040, 34 USPQ2d 1467, 1471 (Fed. Cir. 1995) and *W.L. Gore & Associates Inc., v. Garlock Inc.*, 842 F.2d 1275, 1280, 6 USPQ2d 1277, 1282 (Fed. Cir. 1988). District courts around the United States are also inclined to uphold the use of the term about, including the District of Massachusetts, which recently held that even where the range of the two figures in question were half an order of magnitude apart, it was upheld because the difference was no greater than measurement errors inherent in measurements of that sort. The court also found that the use of the term about means that precise values were not contemplated. See *Minnesota Mining & Manufacturing Co. v. Beutone Specialties Co. Ltd.*, 117 F. Supp.2d 72,88 (Dist. Mass. 1999). See also, MPEP §2173.05(b). Thus, applicants' use of the term about in relation to the pH and the rage of pH from about 5 to about 7 is clear because precise pH conditions were not contemplated, those of skill in the art (the level of those skilled in the art of macrocyclic molecules is quite high) having the benefit of the totality of the disclosure would know how to determine the appropriate pH conditions for their particular purpose.

Claims 10, 12-33, and 59 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the term "hydrocarbon" in Claims 10, 12, 18, and 59 is unclear. The Examiner states that because the definition in the specification on page 16 is repugnant to that known in the art wherein a hydrocarbon is limited to molecules containing only carbon and

hydrogen atoms (see Stedman's Dictionary). On page 16 of the specification and in the claims it is the term "hydrocarbon group" that is defined and used and not the term "hydrocarbon" as the Examiner suggests. The definition of "hydrocarbon group" is not being used contrary to its ordinary meaning and one of skill in the art is reasonably put on notice of its intended use by the definition on page 16. Thus, the term "hydrocarbon group" is not unclear.

Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for describing linking the thioester and the nucleophile; however, the formula in the claim contains an ester, not a thioester. The applicants have corrected typographical error as suggested by the Examiner.

Claims 10, 28-33 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, for using the phrases like "about 4 carbon atoms" and "about 10 heteroatoms" because they are unclear as to their scope. As stated above in regard to the rejections of the pH range, the use of the term about is not fatally ambiguous because a person of ordinary skill in the art would understand the variability based on the totality of the disclosure. As the Examiner points out, the "specification is replete with examples of highly varied substrates with various numbers of carbon atoms." This argument lends support to the applicants' position that based on the totality of the disclosure, one of skill in the art would understand that the number of carbon atoms will vary depending on the particular purpose intended.

Claims 12-33 stand rejected under 35 U.S.C. § 112, second paragraph, because the Examiner asserts that the compound “N-C₂-C₆alkanoylC₂-C₆aminoalkyl” in claims 14 and 22 is unclear because it depends from Claim 12, which is limited to a C₁₋₁₂ alkyl group.

The rejection is traversed.

The language “optionally substituted C₁₋₁₂alkyl group” is sufficiently broad to encompass compounds in which R is “N-C₂-C₆alkanoylC₂-C₆aminoalkyl.” That is, the “N-C₂-C₆alkanoylC₂-C₆aminoalkyl” group is a C₂₋₆alkyl group substituted at the ω carbon (i.e., the terminal methyl carbon) with a carboxamide residue such as a C₁₋₅alkyl-C(O)NH group. However, in the interest of advancing prosecution, claim 12 has been amended to provide that R is optionally substituted C₁₋₁₂alkyl or N-C₂-C₆alkanoylC₂-C₆aminoalkyl. Support for the amendment may be found throughout the specification as filed.

Claims 18-27, 47-48, and 50-55 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because in the limitations of R₁ and R₂ the phrase “the synthetic and biosynthetic amino acid residue side chains” is unclear because the article ---the--- indicates particular residue side chains and none have been particularly defined. Applicants have corrected this formal defect as suggested by the examiner.

Claims 20 and 48 stand rejected under 35 U.S.C. § 112, second paragraph for being indefinite because the limitations of the pH of the side chain, the phrase “about pH 7” is unclear as to its scope. For the reasons give above regarding the rejections of claims 6-8 and 39-41, claims 20 and 48 are not indefinite because the term about does not render a claim ambiguous

because one of ordinary skill in the art would understand the limitation in the context of the specification as a whole.

Claims 28-33 stand rejected under 35 U.S.C. § 112, second paragraph because R_1 and R_2 are not defined. Applicants have defined the term as suggested by the Examiner.

Claims 31 and 33 stand rejected under 35 U.S.C. § 112, second paragraph because the phrase “and the like” is wholly unclear as to the metes and bounds of the limitations of the non-peptidic SPACER. Applicants have deleted the term “and the like” from the claim.

Claim 33 stands rejected under 35 U.S.C. § 112, second paragraph because the limitation of the spacer being non-peptidic is unclear wherein a functional group in the Markush list is glycine, an amino acid. The limitation is not unclear because glycine is not a peptide, but merely a small molecule that happens to be an amino acid. Glycine, without being bound to other amino acids is not a peptide. Thus, the limitation of the spacer being non-peptidic is not unclear.

Claims 34-55 stand rejected under 35 U.S.C. § 112, second paragraph because the term “essentially” in the first step is unclear. The term essentially has been deleted from the claim for the purpose of clarification.

Claims 34-55 stand rejected under 35 U.S.C. § 112, second paragraph because the Examiner asserts that in claim 34 the “contacting” step is unclear because the substrate is contacted with a TE domain protein in the first step, and since heterodimer substrates can be formed in the first step, anything greater than 2 residues would meet the limitations of being the “elongated” substrate. Applicants respectfully point out that the Examiner's assertions are true

and that this is exactly what the applicants claim. In claim 34, the TE domain is recited as being contacted “with a first substrate under conditions conducive to formation of a TE-O-acly substrate intermediate... to form an elongated substrate....” Thus, these claims are not unclear because after this first elongation step, wherein anything greater than two residues would meet the limitation, the elongation step must be repeated until the intermediate substrate oligomer is of sufficient length.

Claim 59 stands rejected under 35 U.S.C. § 112, second paragraph because "can be" is unclear. As suggested by the Examiner, “can be” has been replaced by “is” for clarification.

Accordingly, the rejections to claims 1-55 and 59 under 35 U.S.C. § 112 should be deemed overcome and the claims found allowable.

4. 35 U.S.C. §112, 1st Paragraph Rejections

Claims 1-55 and 59 stand rejected under 35 U.S.C. 112 for containing subject matter which was not described in the specification. The Examiner asserts that claims are directed to methods of cyclizing compounds wherein few structural limitations are imposed with respect to the functional examples. For example, the Examiner asserts that the majority of the substrates used in the cyclization reactions are short peptides (Examples 3-21) or depsipeptides (Examples 22-23), but that the few examples describing the use of peptide substrates does not support the claimed genus so that one of skill in the art would be able to predict the structure of the substrates usable in the claims. Applicants respectfully traverse the rejection of claims 1-55 and

59.

Applicants respectfully point out that it is the entire specification that is used to determine whether or not the written description requirement is met and not just the Examples disclosed in the specification. At page 6, line 17 to page 9, line 18 of the specification, other examples of substrates are given that fully enable and are commensurate with the scope of the claims. Thus, claims 1-55 and 59 are fully described and the specification meets the requirement of 35 U.S.C. 112.

Claims 34-55 stand rejected under 35 U.S.C. § 112, first paragraph because the Examiner asserts that although the genus of methods is discussed in the specification, there is no evidence that any representative species of such a large and varied genus, wherein the elongation step is repeated indefinitely, was in the possession of the inventors at the time of filing. The applicants respectfully traverse this rejection.

Claims 34 – 55 are not directed to methods wherein the elongation step is repeated indefinitely, by is repeated only “until the intermediate substrate is of sufficient length to undergo macrocyclization.” The specification supports this at least at page 10, third paragraph to page 11, first carry over paragraph, where the specification describes that “a pentapeptide substrate typically is not long enough to undergo macrocyclization. Dissociation of the TE domain bound pentapeptide occurs by intermolecular nucleophilic attack of the N-terminal amine functional group from a second pentapeptide substrate to generate a decapeptide substrate dimer that has a sufficiently long linear backbone for TE domain protein catalyzed macrocyclization.... Thus, claims 34 – 55 are fully described under 35 U.S.C. § 112, first

paragraph.

Claims 1-55 and 59 stand rejected under 35 U.S.C. § 112, first paragraph for not reasonably providing enablement for methods using any PKS TE domains with any substrate or methods using NRPS TE domains with any substrate. The Examiner asserts,

“[t]he instant specification describes TE domains as portions of polyketide synthases (PKSs) or non-ribosomal peptide synthetases (NRPS). The examples exclusively use NRPS TE domains; no PKS TE domains are used. The specification describes how excised TE domain a polyketide synthase, DEBS, does not promote cyclization (see specification page 3). No guidance is presented for the use of PKS TE domains, in particular for the substrates necessary for the use of PKS TE domains. The state of the prior art contradicts the claim that excised PKS TE domains promote cyclization. Thus, the predictability of using any substrate with an excised PKS TE domain is extremely low. For all these reasons, the instant claims are not enabled for using PKS TE domains.”

Applicants respectfully traverse this rejection.

Applicants specification is clearly enabled for the scope of the claims by disclosing multiple examples of TE domains appropriate to catalyze the macrocyclization reactions. As the specification states at the top of page 8, substrate specificity of other excised TE domains can be determined by those skilled in the art by routine procedures. Routine procedures are not considered “undue experimentation” as the Examiner asserts. The Applicants then provide guidance to those skilled in the art as to how to select appropriate TE domains and their substrates. In addition, the specification provides many working examples of the claimed methods. Thus, under the Wands factors Applicants have fully enabled the scope of the claims because no undue experimentation is necessary, only routine procedures are needed to determine substrates; Applicants provide guidance in the specification as to how to choose TE domains and

substrates; many working examples are presented; and those of skill in the art are considered highly skilled.

Accordingly, applicants request the withdrawal of these rejections and allowance of the claims.

5. 35 U.S.C. § 102 (a) Rejections

Claims 1-8 and 11 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Trauger *et al.* (Peptide cyclization catalysed by the thioesterase domain of tyrocidine synthetase. Nature. Sept. 2000. 407:215-218). The Examiner considers Trauger *et al* to be “by others” because inventors Burkart and Schwarzer are not authors.

Applicants submit herewith a Rule 131 Declaration that effectively antedates the Trauger, et al., literature publication. Thus, Trauger, et al., is not available as prior art under 35 U.S.C. §102(a) against the claims of the instant application.

Accordingly, applicants request withdrawal of the rejections and allowance of the claims.

CONCLUSION

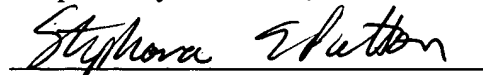
Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants’ attorney would expedite prosecution of this application, the Examiner is cordially

invited to call the undersigned attorney of record.

Applicants request a two-month extension of time. Applicants, however, conditionally petition for an additional month extension to provide for the possibility that such a petition is required. As provided below charge Deposit Account No. **04-1105** for any required fee.

June 30, 2004

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Stephana E. Patton", is written over a horizontal line.

John B. Alexander, Ph.D. (Reg. No. 48,399)
Stephana E Patton, Ph.D. (Reg. No.: 50,353)

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Docket No. 55046 (70207)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S): T. C. Walsh, et al.

EXAMINER: K. M. Kerr

SERIAL NO.: 10/017,324

GROUP: 1652

FILED: December 15, 2001

FOR: METHODS FOR PREPARATION OF MACROCYCLIC MOLECULES
AND MACROCYCLIC MOLECULES PREPARED THEREBY

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

DECLARATION UNDER 37 CFR 1.131

The undersigned declare as follows:

1. We are co-inventors of the above-identified application assigned to the President and Fellows of Harvard College.
2. Prior to September, 2000, we had reduced to practice reactions preparing macrocyclic molecules by contacting an excised thioesterase (TE) domain with a substrate that contained a nucleophile and an activated acyl residue.
3. Prior to September, 2000, we had reduced to practice macrocyclization substrates for use in preparing macrocyclic molecules that contained a nucleophile and an activated thioester group.
4. Prior to September, 2000, such macrocyclization substrates had been contacted in an aqueous media with a purified excised TE domain under conditions conducive to macrocycle formation. As evidence thereof, attached as Exhibit 1 are selected portions of a disclosure of the subject matter of the above-identified application. The disclosure attached as Exhibit 1 was generated, and actual experimental work disclosed therein was performed, prior to September, 2000. Portions of the disclosure attached as Exhibit 1, including specific dates, have been removed.

Walsh, et al.
U.S.S.N. 10/017,324
Page 2

5. We heretofore further declare that all statements made herein are of our own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the above-identified application or any patent issue thereon.

Date: June 10, 2004

John W. Trauger
John W. Trauger

Date: _____

Rahul M. Kohli

Date: _____

Henning D. Mootz

Date: _____

Mohamed A. Marahiel

Date: _____

Christopher T. Walsh

Date: _____

Dirk Schwarzer

Date: _____

Michael D. Burkart

BOS2_442602.1

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Date: _____

John W. Trauger

Date: 6/29/04

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Date: _____

John W. Trauger

Date: _____

Rahul M. Kohli

Date: 11.6.2004

H. Mootz

Henning D. Mootz

Date: 10.6.2004

Mobanef A. Marahiel

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Rahul M. Kohli

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Henning D. Mootz

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Mohamed A. Marahiel

Date: 6/9/14

Christopher Walsh

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Christopher T. Walsh

Date: _____

Dirk Schwarzer

Date: 06/09/2004


Michael D. Burkart

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